Iron Therapy in Pregnancy

A Comparative Study of Various Modes

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• *Study was made of groups of pregnant patients who were given various hematinic agents from the seventh month of gestation to term.*

Dilute hydrochloric acid given with meals in usual doses produced no appreciable increase in the hemoglobin concentration, erythrocyte count or packed cell volume. Iron therapy in the form of orally administered ferrous sulfate, or orally administered ferrous sulfate-molybdenum oxide, or as intravenously administered saccharated iron oxide had a beneficial effect on these three factors in the blood.

INTEREST IN THE STUDY of anemia in pregnancy probably began more than a century ago with the publication of *Notes on Anhæmia* by Walter Channing.[2] He reported the first case which ended fatally and noted in the anamnesis that the patient had been eating a diet adequate in meats, juices and decoctions of meat as well as alcoholic and vinous stimulants. Inasmuch as food was well digested and the appetite remained good, iron therapy, although considered, was believed unnecessary, he reported. Symptoms of the various organ systems of the body were well outlined in the report, especially those concerning the circulatory and respiratory systems. It was noted that the blood was changed, being pale, and "that material which colored the blood, especially the red globules, was changed or more or less wanting. It is more liquide, coagulates but slightly or not at all, hence the composition, its chemical elements or their relations, have undergone changes of some sort. The blood was thin and watery, pale, with soft or no coagula. It resembles somewhat the blood which escapes at length from a wound which cannot be closed, as from pulling a tooth, cutting the gums, etc., in hemorrhagic persons. Yet the blood in anhæmia has its differences from this. In its cause it especially has these, for it is not a state induced by hemorrhage." Increased blood volume in pregnancy was hinted by Channing, for some of his patients were treated by blood letting and the "blood burst from the orifice with violence" and the small veins became large and of "bright arterial color." Transfusion was considered "if safe in itself" but "what possible benefit would such a supply of blood be?"

The seemingly neglected importance of adequate gastric secretion in pregnancy was reported in 1932 by Strauss and Castle[12, 13] in two publications. Groups of patients were subjected to monthly gastric analysis and it was found that there was decreased secretory power of the gastric mucosa in pregnancy and the cause of the decrease was unknown. Eighty per cent of the patients studied had higher concentrations of hydrochloric acid in the gastric juice after delivery than during pregnancy, and the amount was about three times as great as during the sixth month of gestation. A relationship of hemoglobin levels to the adequacy of diet and to the content of hydrochloric acid in the third trimester was noted. Although the hemoglobin levels were generally low, patients with adequate diet and 15 cc. or more of one-tenth normal hydrochloric acid had the highest levels, and patients with achlorhydria and inadequate diet had the lowest. The anemia resembled that of gastrointestinal disturbances, poor diet and loss of blood.

Hamilton, Higgins and Alsop[8] found the use of hydrochloric acid to be of value in treating patients who did not respond to the administration of iron by mouth. Seventy-four per cent of the patients in a series reported upon by them responded well when given iron orally; and when those who did not benefit were given hydrochloric acid as well, the total number with favorable response was increased by another 10 per cent.

The most widely recommended iron preparation for use in hypochromic anemia is ferrous sulfate U.S.P. The dosage needed is smaller than that of reduced iron or ferric salts, and the average dose is 1 gm. daily in divided portions. Occasionally it is ineffective and now and again disagreeable and variable gastrointestinal side-effects develop.[7]

In recent years there has been an almost precipitous rise in the use of iron compounded with other metals for hematinic purposes. Ferrous sulfate processed with molybdenum oxide in tablet form has been favorably reported upon in the literature. Talso and Dieckmann[14] in 1948 reported that various iron

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Presented before the Section on Obstetrics and Gynecology at the 83rd Annual Session of the California Medical Association, Los Angeles, May 9-13, 1954.

salts did not produce significant elevation in hemoglobin concentrations. However, in 1949, Dieckmann and Priddle,[4] noting the favorable results of Healy and Neary in the use of iron-molybdenum complex employed it in their clinic. Subsequently they reported their impressions concerning the use of this material in pregnancy[5] and found that the rise in hemoglobin was so dramatic that at first it was thought the patients might have a decrease in plasma volume, although this impression was discarded upon further deliberation.

In recent years iron preparations that are effective when given intravenously have become available. Nicholson and Assali[10] observed a favorable response to the use of saccharated iron oxide in anemic pregnant patients, and noted the response was greatest in the cases in which anemia was greatest. Kartchner and Holmstrom[9] used iron intravenously with positive results in patients who could not otherwise receive iron or who registered for care so late in pregnancy that therapy with iron by mouth would not be effective. Hamilton, Higgins and Alsop[8] used iron oxide intravenously in a large series of patients and observed favorable response. They also noted several side effects and in some instances felt justified in terminating the therapy.

According to Eastman[6] the increase in the total volume of blood in gestation approximates 30 per cent, the increase in plasma volume is about 40 per cent, and the increase in red cell volume is about 20 per cent. It can be surmised from this that there is a concurrent decrease in the hematocrit reading. The increase in plasma volume has been attributed to hydremia. Frequently in pregnancy anemia is simulated, with relative reduction of packed cell volume, of erythrocyte content and of hemoglobin content. This condition has been called "pseudoanemia," for actually the volume of erythrocytes is increased by 20 per cent. The diagnosis of anemia in pregnancy, according to Eastman, should be made only if the erythrocyte content falls below 3.25 million per cu. mm., the hemoglobin level below 10 gm. per 100 cc., and the packed cell volume below 30 per cent of the whole blood. According to Talso and Dieckmann[14] there is a 25 per cent increase in plasma volume during pregnancy, but the erythrocyte count increases only 23 per cent, the disparity bringing about "physiologic anemia."

The reported "standard values" for hematologic factors in peripheral blood vary somewhat, depending on the authority, but in general there is fairly close agreement as to standards. Talso and Dieckmann used as standard values a hemoglobin level of 10 gm. per 100 cc. of blood, a packed cell volume of 33 per cent of the whole blood and an erythrocyte content of 3,360,000 per cu. mm. of blood. They also noted that errors in hemoglobin determinations were 7 to 15 per cent, that errors in erythrocyte count were about 8 per cent, and that the error in packed cell volume determinations was only 2 per cent. Wolff and Limarzi[15] established values of 10 gm. of hemoglobin per 100 cc. of blood, erythrocyte content of 3,500,000 per cu. mm. and packed cell volume of 30 per cent.

Benstead and Theobald[1] observed that normal values were maintained if patients were given therapeutic doses of iron during pregnancy, and also that ferrous sulfate or ferrous sulfate-molybdenum oxide complex given during the last trimester produced a recovery from anemia and a maintenance of values to term.

The therapy of choice varies. Some investigators have reported that ferrous sulfate is as adequate as any form[1] while others have expressed belief that ferrous sulfate-molybdenum oxide complex is necessary.[3, 5] Hamilton, Higgins and Alsop[8] reported that the addition of hydrochloric acid to the intake of ferrous sulfate-molybdenum oxide complex brought about favorable response in the levels of blood components. Lund advocated the addition of vitamin C as a hematinic because it aids in the absorption of iron. Recently many investigators[8,9,10] have reported that administration of saccharated oxide of iron has produced remarkable improvements in the condition of peripheral blood of anemic pregnant patients.

The current prevalent practice is to administer iron alone or in some combined form during pregnancy. Some obstetricians give it throughout pregnancy without doing laboratory studies on the peripheral blood, while others carefully and frequently determine the condition of the blood and use iron only if indicated. Probably the majority of physicians use iron preparations for all or part of the pregnancy and examine the blood periodically only if there is clinical indication of anemia. One of the authors (R.W.D.) long maintained that the routine administration of iron by mouth during pregnancy was of little or no value because of the various factors involved in "pseudoanemia" as previously mentioned, and did not employ any form of iron intake with the exception of that ingested in the diet. This opinion was not isolated, as other practitioners felt also at one time that supplementation of the diet by iron salts was of slight or no value.[4]

Accordingly a study was begun to test the opinion that the routine use of iron therapy in pregnancy either with or without careful laboratory observations of the blood was of little or no value, to review the great number of basic factors in the increase of values in the peripheral blood in pregnancy as outlined in preceding paragraphs, and to evaluate current widely accepted practices concerning hematinic therapy. Obstetrical patients treated in private practice were divided into five groups in a non-selected manner. All patients were instructed as

TABLE 1.—*Mean erythrocyte count (in millions per cu. mm. of blood)*

Therapy used	No. of patients	7 months	Term	Change	
None	26	3.859	4.029	+.170	Combined variance of changes
Hydrochloric acid	30	3.869	4.008	+.139	
Ferrous sulfate	27	3.794	4.345	+.551	
Fesmocox*	24	3.733	4.210	+.477	$S^2 = .2358$
Saccharated iron oxide	20	3.640	4.103	+.463	$S = .4856$

*Ferrous sulfate and molybdenum oxide complex.

TABLE 2.—*Mean hemoglobin (in gms. per 100 cc. of blood)*

Therapy used	No. of patients	7 months	Term	Change	
None	26	10.15	11.51	+1.36	Combined variance of changes
Hydrochloric acid	30	10.57	11.64	+1.07	
Ferrous sulfate	27	10.61	13.09	+2.48	
Fesmocox*	24	10.68	12.94	+2.26	$S^2 = 1.611$
Saccharated iron oxide	20	9.97	12.38	+2.41	$S = 1.27$

*Ferrous sulfate and molybdenum oxide complex.

TABLE 3.—*Mean packed cell volume (per cent)*

Therapy used	No. of patients	7 months	Term	Change	
None	26	34.0	37.3	+3.3	Combined variance of changes
Hydrochloric acid	30	34.5	37.1	+2.6	
Ferrous sulfate	27	34.9	40.2	+5.3	
Fesmocox*	24	35.0	40.5	+5.5	$S^2 = 12.113$
Saccharated iron oxide	20	32.5	38.4	+5.9	$S = 3.48$

*Ferrous sulfate and molybdenum oxide complex.

TABLE 4.—*Mean color index†*

Therapy used	No. of patients	7 months	Term	Change	
None	26	.909	.965	+.056	Combined variance of changes
Hydrochloric acid	30	.946	.993	+.047	
Ferrous sulfate	27	.963	1.020	+.057	
Fesmocox‡	24	.971	1.042	+.071	$S^2 = .016632$
Saccharated iron oxide	20	.941	1.025	+.084	$S = .1290$

†Color index $= \dfrac{\text{Hemoglobin grams per 100 cc.} \times 6.9}{\text{Erythrocytes millions per cu. mm.} \times 20 \text{ (Wintrobe)}}$

‡Ferrous sulfate and molybdenum oxide complex.

to diet adequate in calories, vitamins, protein, carbohydrate and fat. In addition they were told to drink one quart of skimmed milk and to take one multiple vitamin capsule daily. Adherence to diet and other prescription was under meticulous and personal control. Each patient, when the gestation period reached seven months, was assigned to either a control or treatment group. Laboratory determination of the hemoglobin concentration, packed cell volume and erythrocyte content of the peripheral blood was carried out.

The first group of patients (Group I) consisted of 26 who received no supplemental hematinic therapy of any sort. Group II was made up of 30 patients who received 0.6 cc. of dilute hydrochloric acid three times daily with meals. Patients in these two groups received no iron therapy as such. Group III consisted of 27 patients who received three times daily, with meals, 1 gm. in divided portions of enteric coated (and, incidentally, iron protective coated) ferrous sulfate U.S.P. In Group IV were 24 patients who received two enteric and iron protective coated tablets containing each 0.195 gm. of ferrous sulfate and 0.003 gm. of molybdenum oxide three times daily with meals. Group V consisted of 20 patients who received saccharated iron oxide intravenously during the last two months of pregnancy. The dosage given was calculated on the basis of the hemoglobin deficiency. One hundred milligrams of elemental iron (or one 5.0 cc. ampoule) was injected intravenously for each 0.6 gram deficit of hemoglobin per 100 cc. of blood, and the dosage did not take into account the increase in blood volume. The various treatments described were begun on all patients at seven months of gestation regardless of the presence or absence of anemia, with the prime objective of determining whether there would be any differences in the various findings in the peripheral blood associated with the routine use of the various agents of therapy. When the patients reached term, as determined by the onset of labor, the various laboratory studies were repeated.

The data obtained in all groups were subjected to analysis. Table 1 contains the figures for the mean erythrocyte count in millions per cu. mm. of blood at the seven-month period and again at term. Table 2 gives similar data as to mean hemoglobin levels. Table 3 similarly contains the mean figures for the packed cell volume, and the mean values of the color index are given in Table 4. The standard deviation was then calculated according to the formula

$$S^2 = \frac{\Sigma d^2 - \frac{(\Sigma d)^2}{N}}{N - 1}$$

wherein

S^2 = (standard deviation)^2
N = number of patients in group
Σd = sum of the differences of each observation from seven months to term
Σd^2 = sum of the same differences squared

RESULTS

There was an increase in all the mean values from the time the patients were observed initially until the time labor commenced. The erythrocyte count (Table 1) increased in all groups including the control group and the group made up of patients who received hydrochloric acid. However, patients in the three groups in which specific iron therapy of one kind or another was given had a much greater increase in erythrocyte count. The mean hemoglobin level increased in all groups also, and similarly there was a much greater rise in patients who received

some form of iron as compared with those who were in either the control group or the group in which hydrochloric acid only was given. The mean packed cell volume likewise rose higher in the patients who received some form of iron therapy as compared with those in control groups or in groups receiving hydrochloric acid only. In none of the five groups, however, was there any significant change in the values of the color index; indeed, the color indices varied little from group to group.

By the method of Scheffé it was determined statistically that the differences in gains in all four variables (erythrocyte count, hemoglobin content, packed cell volume and color index) as between the three groups of patients treated with some form of iron were not sufficiently large (compared to the natural variation in gain from patient to patient) to be significant at the 5 per cent level. There was therefore no basis for concluding that any of the three iron preparations used is better, or worse, than any of the others. Likewise the difference in gains on the same four variables between the two groups not receiving iron were too small to justify conclusion that there was any true difference between the group receiving hydrochloric acid and the group receiving no therapy (control group) with respect to these hematological variables.

On the other hand, as to three of the variables—erythrocyte count, hemoglobin content and cell volume—the gains of patients receiving some one of the three forms of iron therapy were significantly larger, at the 5 per cent level, than the gains of patients in the two groups not receiving iron.

DISCUSSION

The beginning premise that supplemental iron therapy in the last part of pregnancy is of little or no value was found to be not true. Patients who received iron therapy as compared with the two groups of patients receiving no iron—the control group and the group receiving hydrochloric acid—had relatively greater response as regards erythrocyte count, hemoglobin level and packed cell volume. There was no significant difference as to color index between the control groups (hydrochloric acid and control groups) and the groups in which treatment with iron was given. This is to be expected when one considers the factors involved in the color index—namely, hemoglobin and numbers of erythrocytes plus the utilization of a constant factor. When the color

$$\text{index} = \frac{\text{hemoglobin grams per 100 cc.} \times 6.9}{\text{erythrocytes millions per cu. mm.} \times 20},$$

it is obvious that when groups of patients are given treatment which increases both hemoglobin and the number of erythrocytes, there may not be a great change in the color index.

Side effects of the various preparations that were used were of more than passing interest. In only one case was it necessary to stop treatment because of gastrointestinal intolerance to ferrous sulfate, and in no case because of intolerance to ferrous sulfate-molybdenum oxide complex. There were few unfavorable reactions to intravenous use of saccharated iron oxide. One patient had syncope once but it did not recur on subsequent injections. Two patients noted giddiness or lightheadedness on one occasion. There were a number of patients in whom sore antecubital fossae, containing hematomas developed, but none requested discontinuance of therapy. An interesting side effect of the use of hydrochloric acid was that in many cases patients who had heartburn without the medication were relieved of this common disorder of pregnancy after they began taking it. Perhaps heartburn is due to achlorhydria, a condition present in many pregnant women, as was noted by Strauss and Castle. This observation will be subjected to further study.

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